become activated by said peptide or polypeptide, which T cells will then accumulate at said site.

B9

REMARKS

Claims 1-46 presently appear in this case. Claims 2-7, 9, 11-19, 21, 23, 26-29, 32, 34-42 and 45 have been withdrawn from consideration. No claims have been allowed. The official action of July 30, 2002, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a method for inhibiting neuronal degeneration caused or exacerbated by glutamate toxicity in the central nervous system of an individual in need thereof. The inhibition is attained by causing activated T cells, which have been activated by Cop 1 or a Cop 1-related peptide or polypeptide, to accumulate at the site of neuronal degeneration in the individual in need. This causes inhibition of neuronal degeneration at that site. The individual being treated is other than one who has multiple sclerosis. The activated T cells may be caused to accumulate at the site of neuronal degeneration either by adoptive transfer of activated T cells, which have been activated by Cop 1 or a Cop 1-related peptide or polypeptide, or by active immunization with Cop 1 or a Cop 1-related peptide or polypeptide *in vivo*, thereby causing T cells to

become activated by the peptide or polypeptide, which will then accumulate at the site. Central nervous system cells may be protected from glutamate toxicity by this method, and injuries or diseases caused or exacerbated by glutamate toxicity may be treated by this method.

With respect to the restriction requirement, the examiner states that because applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse. It is urged, however, that applicants explicitly stated that the election was with traverse and applicants distinctly and specifically explained why the election requirement was no longer applicable in view of the addition of new independent claim 43, which is a true generic linking claim. The argument was that the linking claim obviated the restriction requirement. This is a valid traversal, and the examiner has no right to treat this election as being without traverse. If it is necessary to file a petition on the restriction requirement, then the Commissioner will determine whether the election was with or without traverse.

The examiner states that applicants have not explained to the examiner why any of the restricted groups should be rejoined to the elected Group IV in light of the

linking claim. Again, this statement of the examiner is respectfully traversed. The paragraph bridging pages 6 and 7 of applicants' response of May 13, 2002, clearly explained why claim 43 was generic to the methods of claims 1 and 20. Furthermore, new dependent claims 45 and 46 clearly established that the claim was generic to causing the T cells to accumulate at the desired site by administering the T cells or by administering Cop 1 or a Cop 1-related peptide or polypeptide.

The examiner has rejoined Groups I and IV. However, the examiner's reasoning for this particular rejoinder was not provided, nor was reasoning provided why Groups II and III were not also rejoined. The examiner has not explained why Groups II and III are patentably distinct from the new combined Group I and IV. Neither has the examiner explained why the inventions of Groups II and III are not encompassed by the generic claim 43. Group I is directed to the administration of activated T cells. Group IV is directed to the administration of Cop 1. Thus, the examiner has conceded that administering Cop 1 activated T cells or administering Cop 1 is the same invention and that these groups are linked by claim 43. Furthermore, claim 1 is drawn to a method for protecting central nervous system cells from glutamate toxicity, while Group IV is directed to a method for treating

injury or disease caused or exacerbated by glutamate toxicity. By joining these groups, the examiner has conceded that both of these methods are directed to the same invention. How then can the examiner possibly take the position that Group II is patentably distinct from Group I, in view of the fact that the examiner has already conceded that administering Cop 1 is not patentably distinct from administering Cop 1 activated T cells? The same is true with respect to Groups III and IV. If Groups I and IV are directed to the same invention, then Groups III and IV must be directed to the same invention. Accordingly, reconsideration and withdrawal of this restriction requirement are respectfully urged.

The examiner has withdrawn claims 2-7, 9, 11-19, 21, 23, 26-29, 32, 34-42 and 45 from further consideration until such time as an allowable generic or linking claim is found. However, it is not understood why claim 7 was withdrawn from consideration. Claim 30 is similar to claim 7 but has been examined. Claim 7 is generic to the elected species. Accordingly, claim 7 should have been examined. Furthermore, claims 11-14 and 34-37 have now been amended to clarify that they are all intended to be generic to Cop 1. Thus, as amended, all of these claims are also directed to the elected species and should be examined. Only claims 2-6, 9, 15-19, 21, 23, 26-29, 32, 38-42 and 45 should be withdrawn from

further consideration until an allowable generic claim is found, after which all of those claims should be examined in this case.

The examiner has objected to the disclosure because a patent application referenced on page 55, line 12, needs to have its status updated. Further, the examiner states that the title of the invention is not descriptive and should be directed to the treatment of glaucoma.

The disclosure at page 55, line 12, has now been amended to substitute the patent number for the application number previously appearing. As to the title, it is too early to determine the breadth of the invention to which allowable claims will be directed. It is requested that this requirement be held in abeyance until allowable subject matter is indicated.

Claims 1, 8, 10, 20, 22, 30, 31, 33, 43, 44 and 46 have been objected to as reciting non-elected species and groups. Appropriate correction has been required. This objection is respectfully traversed.

The non-elected species are non-elected pursuant to an election requirement. If at the end of the day the elected species is found to be allowable, then the examiner will have to examine all of the species encompassed by those claims. The present response shows why the elected species is

allowable. Thus, this objection is premature. Reconsideration and withdrawal thereof are respectfully urged.

Claims 8, 10, 22, 34, 35, 43, 44 and 46 have been rejected under the first paragraph of 35 U.S.C. §112 for lack of enablement of the full breadth of the claims. The examiner states that due to the large quantity of experimentation necessary to determine which cell types are inhibited from neuronal degeneration, to inhibit primary neuronal degeneration of any cell, and to determine whether or not the T cells accumulating at the site of neuronal degeneration are activated by Cop 1, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope. This rejection is respectfully traversed.

As to the examiner's comment that the skilled artisan would not be able to predict whether the lymphocytes observed at the site of injury are activated by Cop 1 since other endogenous antigens may be present at the site of injury, the examiner's attention is invited to the present specification at page 65, where it states:

> The passive transfer of Cop 1-reactive T cells in the present study also caused a significant accumulation of the injected T cells at the site of injury relative to the accumulation of endogenous anti-MBP T cells in the PBS-treated injured rats. [Emphasis added]

It is therefore apparent that if T cells are not administered, the amount of endogenous T cells at the injury site is much smaller than when Cop 1-reactive T cells are administered. Thus, the larger number of T cells at the site of injury must be the injected Cop 1 activated T cells. In this regard, the examiner's attention is also invited to the attached publication of Kipnis et al, "T cell immunity to Copolymer 1 confers neuroprotection on the damaged optic nerve: Possible therapy for optic neuropathies", Proc Natl Acad Sci 97:7446-7451 (2000), which is a publication from the laboratory of the present inventors published after the effective filing date of the present application. Note, where it states at the second column of page 7450:

> It should be noted that the method used here to assess T cell accumulation involved the use of antibodies to the TCR. Using this approach, it is not possible to determine whether the accumulated T cells detected in the nerve are the ones that were injected. In our earlier studies we showed, however, that the injected activated T cells are indeed the ones that accumulate (18).

Reference 18 is Hirschberg et al, J Neurimmunol 89:88-96 (1998). In view of this evidence, there is insufficient reason to doubt the accuracy of applicants' statement that the T cells which are accumulating are, indeed, the Cop 1 activated T cells.

With respect to which cell types are inhibited from neuronal degeneration, the cell type is neurons. The present claims are clear in this regard. Thus, it is requested that this point of the examiner be withdrawn.

As to the examiner's comment about primary neuronal degeneration, the examiner seems to accept that secondary neuronal degeneration is inhibited. If secondary neuronal degeneration is inhibited and there is an on-going insult to the neurons, i.e., on-going primary degeneration, it would be expected that the primary degeneration would be inhibited in the same way that the secondary degeneration is. The examiner has not set forth any reason why one of ordinary skill in the art would not expect that the presently-claimed treatment would also inhibit primary neuronal degeneration. Accordingly, there is insufficient reason to doubt the statements of effectiveness in the present specification for the full scope of the invention. Reconsideration and withdrawal of this rejection are, therefore, respectfully urged.

Claims 1, 8, 10, 20, 22, 24, 25, 30, 31, 33, 43, 44 and 46 have been rejected under 35 U.S.C. §112, second paragraph. The examiner states that the acronym "Cop-1" renders the claims vague and indefinite. Further, the examiner states that claim 1 is indefinite because it does not

have a step that relates back to the preamble. Finally, the examiner states that claims 22, 24, 25, 43 and 44 are incomplete for omitting essential steps, i.e., the administration of a compound, peptide, T cells, etc., to an individual to cause activated T cells to accumulate at the site of neuronal degeneration. This rejection is respectfully traversed.

The claims have now been amended to change "Cop 1" to read "Copolymer 1" wherever it appears, thus obviating this part of the rejection. Furthermore, claim 1 has been amended to state that the active steps cause protection of CNS cells from glutamate toxicity, thus obviating this part of the rejection.

However, the part of the rejection stating that claim 43 is incomplete is respectfully traversed. Claim 43 includes the step of "causing activated T cells ... to accumulate at the site of neuronal degeneration." This is a positive step and includes everything that is essential. The examiner's suggestion of specifying the administration of a compound, peptide or T cells relates only to mere examples of how this causing step takes place. There is no omitted step. The only essential step is present. MPEP §2172.01 is inapposite. The invention will work regardless of the means for getting the activated T cells to the site of injury.

Thus, nothing essential is unclaimed. Reconsideration and withdrawal of this part of the rejection are respectfully urged.

Claim 1 has been rejected under 35 U.S.C. §102(b) as being anticipated by Johnson. The examiner states that Johnson teaches subcutaneous administration of Cop 1 for the treatment of remitting-relapsing multiple sclerosis.

Claim 1 has now been amended to add a proviso that the individual in need is other than one who has multiple sclerosis. Accordingly, this rejection is no longer applicable. Reconsideration and withdrawal thereof are respectfully urged.

Claims 20, 30, 31 and 33 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Johnson in view of Pitt. The examiner states that Johnson teaches administration of Cop 1 to patients with MS, but teaches nothing about glutamate toxicity. The examiner states that Pitt teaches that increased glutamate levels have been in the cerebral spinal fluid of patients with CNS inflammatory diseases, such as MS. The examiner considers it obvious to administer Cop 1 to individuals with MS as taught by Johnson because glutamate toxicity is involved in the pathogenesis of MS as taught by Pitt. This rejection is respectfully traversed.

Claim 20 has now been amended to state that the person being treated is one other than one who has MS. Accordingly, this rejection, as well, has been obviated. Reconsideration and withdrawal thereof is respectfully urged.

The art cited but not applied by the examiner has been noted, as has the examiner's implicit recognition that it is insufficiently pertinent to warrant its application against the claims.

It is submitted that all the claims now present in the case clearly define over the references of record. Reconsideration and allowance are, therefore, earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By Roger L. Browdy by Allen Yun
Roger L. Browdy
Registration No. 25,618
Reg. No. 37,971

RLB:rd
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
G:\BN\B\BENA\Eis-Schwartz18\Pto\AmendmentB.doc

Version with Markings to Show Changes Made

In the Specification

The paragraph beginning at page 55, line 10, has been amended as follows:

In another embodiment, mononuclear phagocyte cells according to PCT Publication No. WO 97/09985 and U.S. patent ~~application Serial No. 09/041,280, filed March 11, 1998,~~no. 6,267,955 are injected into the site of injury or lesion within the CNS, either concurrently, prior to, or following parenteral administration of Cop 1-activated T cells, Cop 1 or a Cop 1-related peptide or polypeptide.

In the Claims

Claims 1, 3, 7-20, 26, 30-43, 45 and 46 have been amended as follows

1 (Amended). A method for protecting central nervous system (CNS) cells from glutamate toxicity, which comprises administering to an individual in need thereof an effective amount of:

(a) activated T cells which have been activated by ~~Cop 1~~Copolymer 1 or a ~~Cop 1~~Copolymer 1-related peptide or polypeptide~~;~~, or

(b) ~~Cop 1~~Copolymer 1 or a ~~Cop 1~~Copolymer 1-related peptide or polypeptide,

thereby protecting CNS cells from glutamate toxicity, with the proviso that the individual in need is other than one who has multiple sclerosis.

3 (Amended). A method in accordance with claim 1, wherein said administering step comprises administering to said individual an effective amount of activated T cells which have been activated by ~~Cop-1~~Copolymer 1 or a ~~Cop-1~~Copolymer 1-related peptide or polypeptide.

7 (Amended). A method in accordance with claim 1, wherein said administering step comprises administering to an individual in need thereof an effective amount of ~~Cop-1~~Copolymer 1 or a ~~Cop-1~~Copolymer 1-related peptide or polypeptide.

8 (~~Amended~~Twice-amended). A method in accordance with claim 46, wherein said ~~Cop-1~~Copolymer 1 or a ~~Cop-1~~Copolymer 1-related peptide or polypeptide is ~~Cop-1~~Copolymer 1.

9 (Twice-amended~~Amended~~). A method in accordance with claim 46, wherein said ~~Cop-1~~Copolymer 1 or a ~~Cop-1~~Copolymer 1-related peptide or polypeptide is a ~~Cop-1~~Copolymer 1-related peptide or polypeptide.

10 (Twice-amended~~Amended~~). A method in accordance with claim 46, in which said ~~Cop-1~~Copolymer 1 or a ~~Cop-1~~Copolymer 1-related peptide or polypeptide is administered in

a manner which promotes active immunization of the individual so as to build up a critical T cell response.

11 (Twice-amended~~Amended~~). A method in accordance with claim 46, wherein said Copolymer 1 or ~~Cop-1~~Copolymer 1-related peptide or polypeptide is a random copolymer that cross-reacts functionally with myelin basic protein (MBP) and is capable of competing with MBP on the MHC class II molecule in antigen presentation.

12 (Amended). A method in accordance with claim 11, wherein said random copolymer comprises one amino acid residue selected from each of at least three of the following groups:

(a) lysine and arginine;

(b) glutamic acid and aspartic acid;

(c) alanine and glycine; and

(d) tyrosine and tryptophan.

13 (Amended). A method in accordance with claim 12, wherein said random copolymer ~~contains~~ consists of four different amino ~~acids~~acid residues, each from a different one of the groups (a) to (d).

14 (Amended). A method in accordance with claim 13, wherein said four different amino acid residues~~acids~~ are alanine, glutamic acid, lysine and tyrosine.

15 (Amended). A method in accordance with claim 14, wherein said random copolymer ~~contains~~ consists of three

different amino acid residues~~acids~~, each from a different one of three groups (a) to (d).

16 (Amended). A method in accordance with claim 15, wherein said ~~random copolymer contains~~three different amino acid residues are tyrosine, alanine, and lysine.

17 (Amended). A method in accordance with claim 15, wherein said three different amino acid residues are~~random copolymer contains~~ tyrosine, glutamic acid and lysine.

18 (Amended). A method in accordance with claim 15, wherein said three different amino acid residues are~~random copolymer contains~~ lysine, glutamic acid, and alanine.

19 (Amended). A method in accordance with claim 15, wherein said three different amino acid residues are~~random copolymer contains~~ tyrosine, glutamic acid, and alanine.

20 (Amended). A method for treating injury or disease caused or exacerbated by glutamate toxicity, which comprises administering to an individual having an injury or disease caused or exacerbated by glutamate toxicity an effective amount of:

(a) activated T cells which have been activated by ~~Cop-1~~Copolymer 1 or a ~~Cop-1~~Copolymer 1-related peptide or polypeptide~~;~~, or

(b) ~~Cop-1~~Copolymer 1 or a ~~Cop-1~~Copolymer 1-related peptide or polypeptide,

with the proviso that the individual having an injury or disease caused by glutamate toxicity is other than one who has multiple sclerosis.

26 (Amended). A method in accordance with claim 20, wherein said administering step comprises administering to said individual an effective amount of activated T cells which have been activated by ~~Cop-1~~Copolymer 1 or a ~~Cop-1~~Copolymer 1-related peptide or polypeptide.

30 (Amended). A method in accordance with claim 20, wherein said administering step comprises administering to an individual in need thereof an effective amount of ~~Cop-1~~Copolymer 1 or a ~~Cop-1~~Copolymer 1-related peptide or polypeptide.

31 (Amended). A method in accordance with claim 30, wherein said ~~Cop-1~~Copolymer 1 or a ~~Cop-1~~Copolymer 1-related peptide or polypeptide is ~~Cop-1~~Copolymer 1.

32 (Amended). A method in accordance with claim 30, wherein said ~~Cop-1~~Copolymer 1 or a ~~Cop-1~~Copolymer 1-related peptide or polypeptide is a ~~Cop-1~~Copolymer 1-related peptide or polypeptide.

33 (Amended). A method in accordance with claim 30, in which said ~~Cop-1~~Copolymer 1 or a ~~Cop-1~~Copolymer 1-related peptide or polypeptide is administered in a manner which

promotes active immunization of the individual so as to build up a critical T cell response.

34 (Amended). A method in accordance with claim 20, wherein said Copolymer 1 ~~Cop-1~~Copolymer 1-related peptide or polypeptide is a random copolymer that cross-reacts functionally with myelin basic protein (MBP) and is capable of competing with MBP on the MHC class II molecule in antigen presentation.

35 (Amended). A method in accordance with claim 34, wherein said random copolymer comprises one amino acid residue selected from each of at least three of the following groups:

(a) lysine and arginine;

(b) glutamic acid and aspartic acid;

(c) alanine and glycine; and

(d) tyrosine and tryptophan.

36 (Amended). A method in accordance with claim 35, wherein said random copolymer ~~contains~~ consists of four different amino ~~acids~~acid residues, each from a different one of the groups (a) to (d).

37 (Amended). A method in accordance with claim 36, wherein said four different amino acid residues~~acids~~ are alanine, glutamic acid, lysine and tyrosine.

38 (Amended). A method in accordance with claim 37, wherein said random copolymer consists of~~contains~~ three

different amino acid residues~~acids~~, each from a different one of three groups (a) to (d).

39 (Amended). A method in accordance with claim 38, wherein said ~~random copolymer contains~~three different amino acid residues are tyrosine, alanine, and lysine.

40 (Amended). A method in accordance with claim 38, wherein said three different amino acid residues are~~random copolymer contains~~ tyrosine, glutamic acid and lysine.

41 (Amended). A method in accordance with claim 38, wherein said three different amino acid residues are~~random copolymer contains~~ lysine, glutamic acid, and alanine.

42 (Amended). A method in accordance with claim 38, wherein said three different amino acid residues are~~random copolymer contains~~ tyrosine, glutamic acid, and alanine.

43 (~~New~~Amended). A method for inhibiting neuronal degeneration caused or exacerbated by glutamate toxicity in the central nervous system (CNS) of an individual in need thereof, comprising causing activated T cells, which have been activated by ~~Cop-1~~Copolymer 1 or a ~~Cop-1~~Copolymer 1-related peptide or polypeptide, to accumulate at the site of neuronal degeneration in the individual in need, thereby inhibiting neuronal degeneration at that site, with the proviso that the individual in need is other than one who has multiple sclerosis.

45 (Amended~~New~~). A method in accordance with claim 43, wherein said activated T cells are caused to accumulate at said site by administering to the individual in need an effective amount of activated T cells which have been activated by ~~Cop-1~~Copolymer 1 or a ~~Cop-1~~Copolymer 1-related peptide or polypeptide.

46 (Amended~~New~~). A method in accordance with claim 43, wherein said activated T cells are caused to accumulate at said site by administering to the individual in need an effective amount of ~~Cop-1~~Copolymer 1 or a ~~Cop-1~~Copolymer 1-related peptide or polypeptide *in vivo*, thereby causing T cells to become activated by said peptide or polypeptide, which T cells will then accumulate at said site.